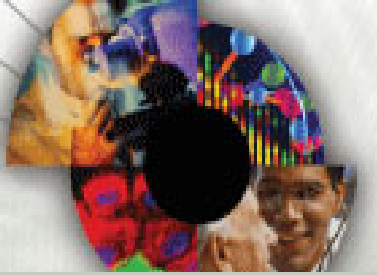
Image-Based Assessment Modalities Pathway Example

Sunday, November 9, 2008

Session: Imaging Pathway — Imaging Approaches to Cancer Detection/ Imaging and Therapy

Scientific
Co-Chairs: Dr. Sam Gambhir & Dr. Maryellen Giger
Dr. Charles Erlichman & Dr. David Mankoff
Advocate
Co-Chairs: Ms. Peggy Devine & Ms. Christie Pratt
Ms. Catherine Huffman & Ms. Patty Lee

5 Domains per Pathway

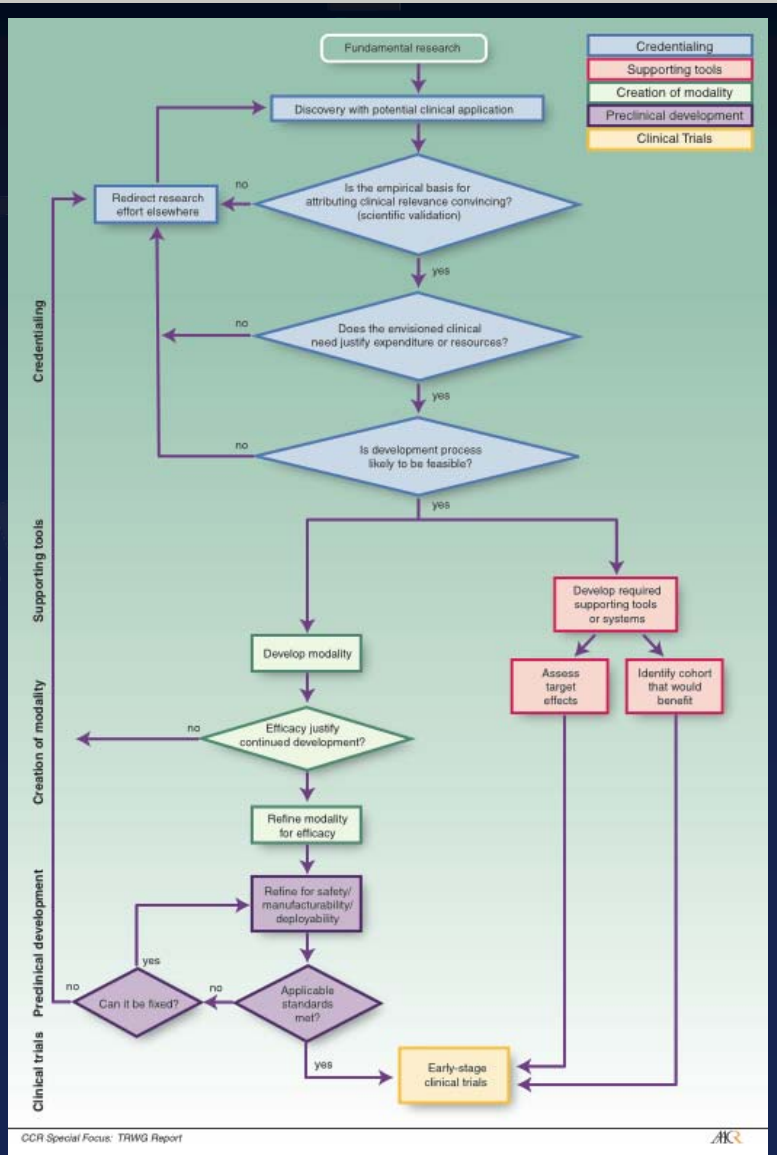


Credentialing

What is the question that imaging will address? assessment of scientific validity, clinical need & feasibility

Creation of Modality

e.g., imaging probes and imaging devices, standardization & multi-site validation



Supporting Tools

e.g., common methods for image data analysis, mechanisms for distribution of probes

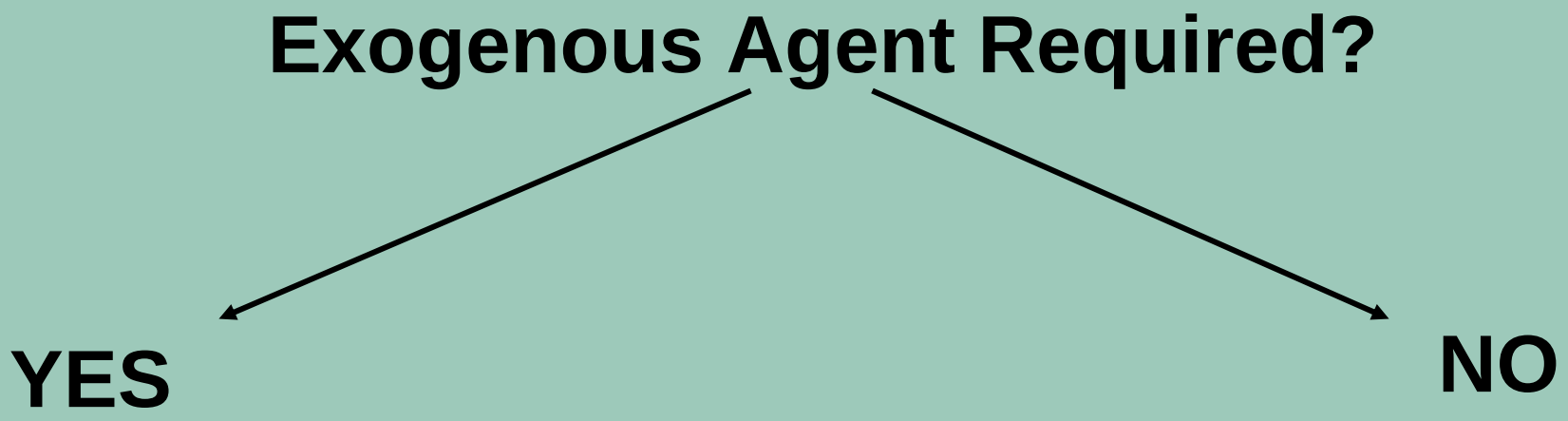
Preclinical Development

e.g., toxicology, biodistribution dosimetry, test on phantoms, IND, IDE

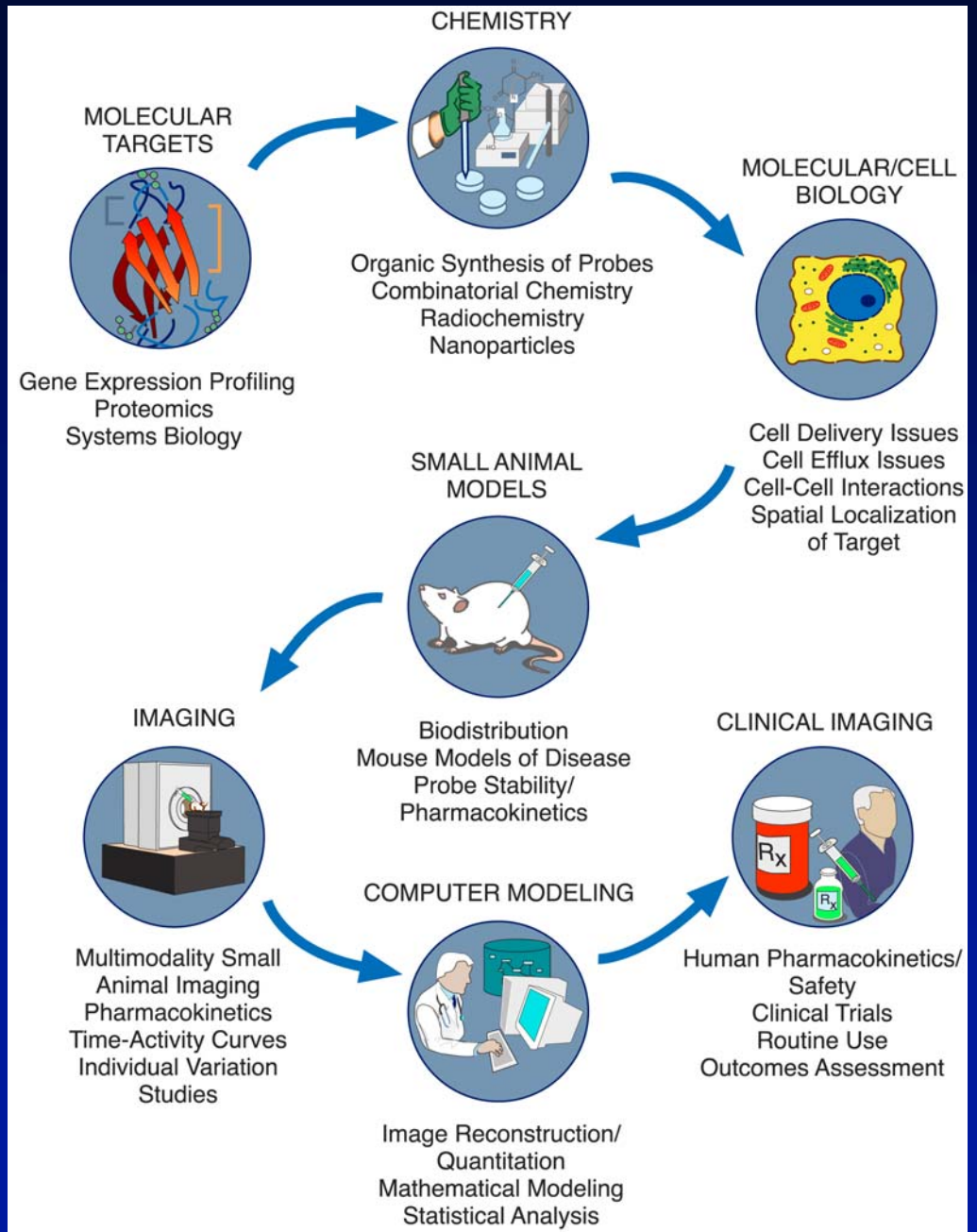
Early Phase Clinical Trials

Biomedical Imaging Background

Imaging Strategy

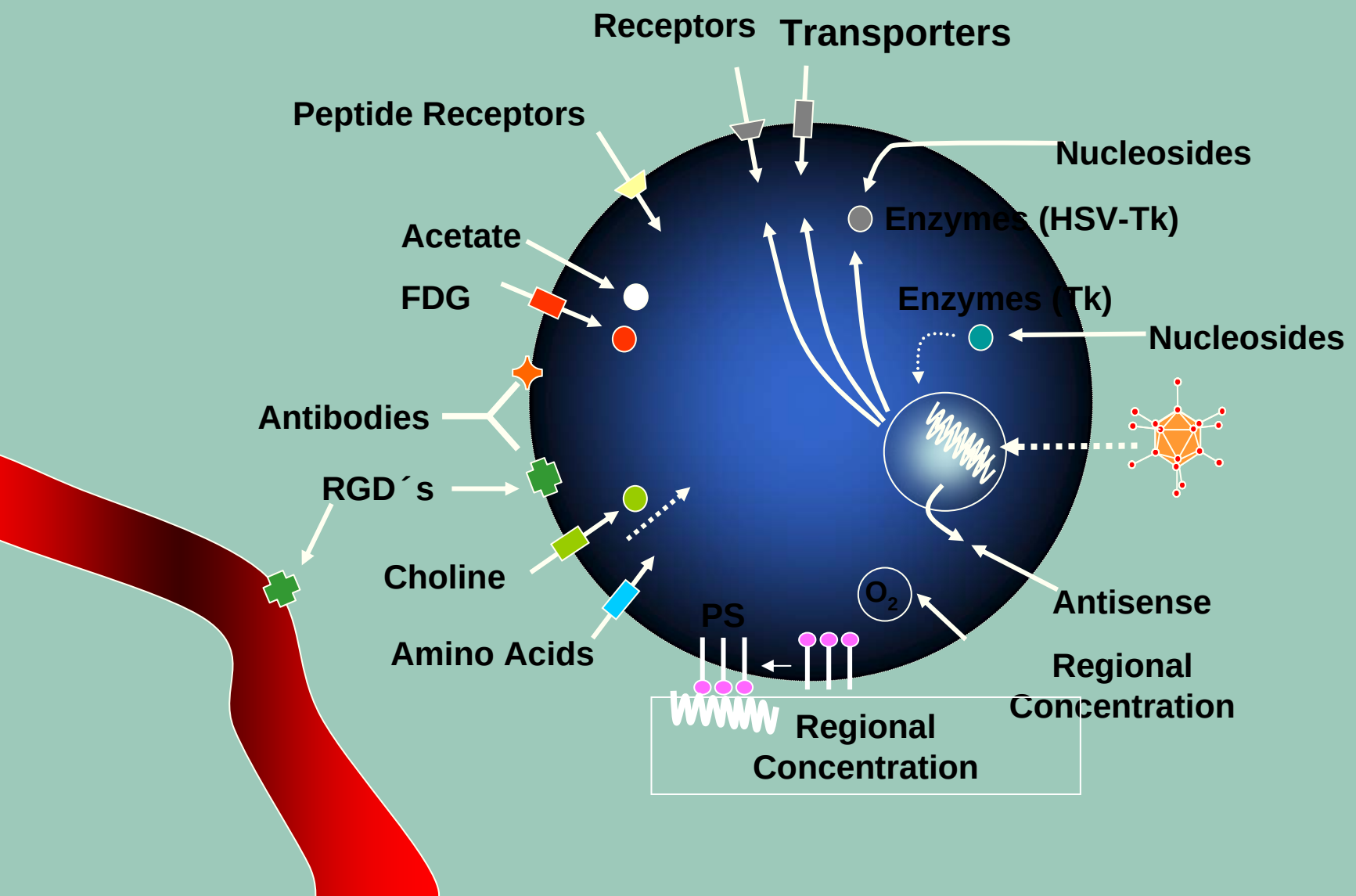


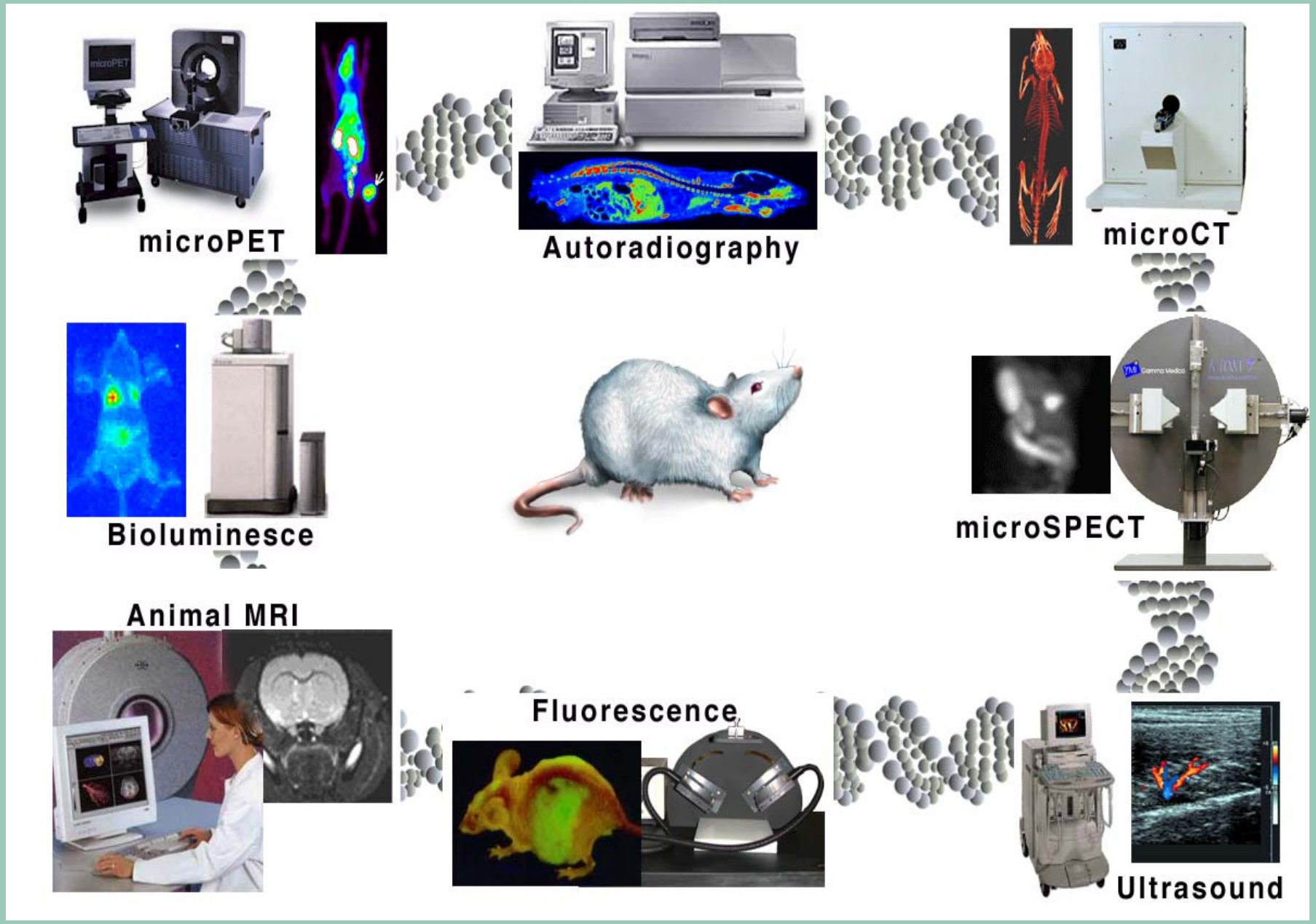
Molecular Imaging Research Chain



Gambhir SS., Principles of Molecular Imaging

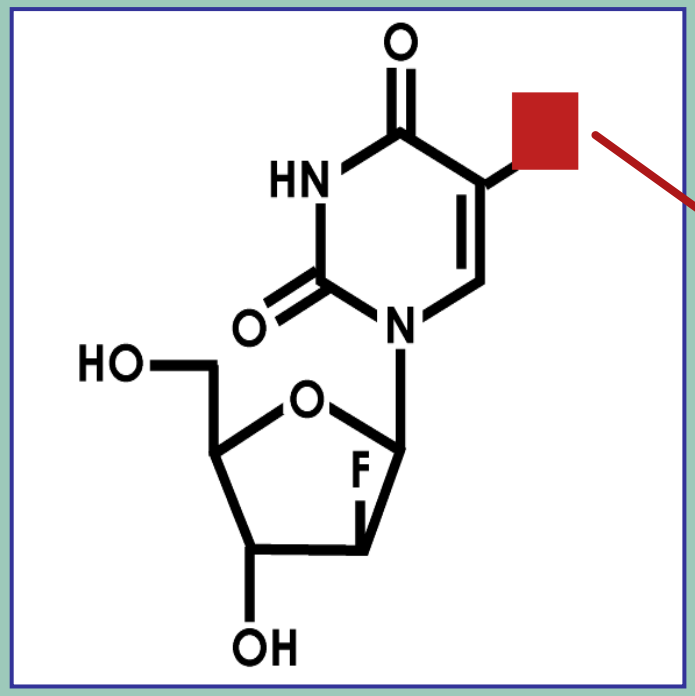
Molecular Imaging in Oncology

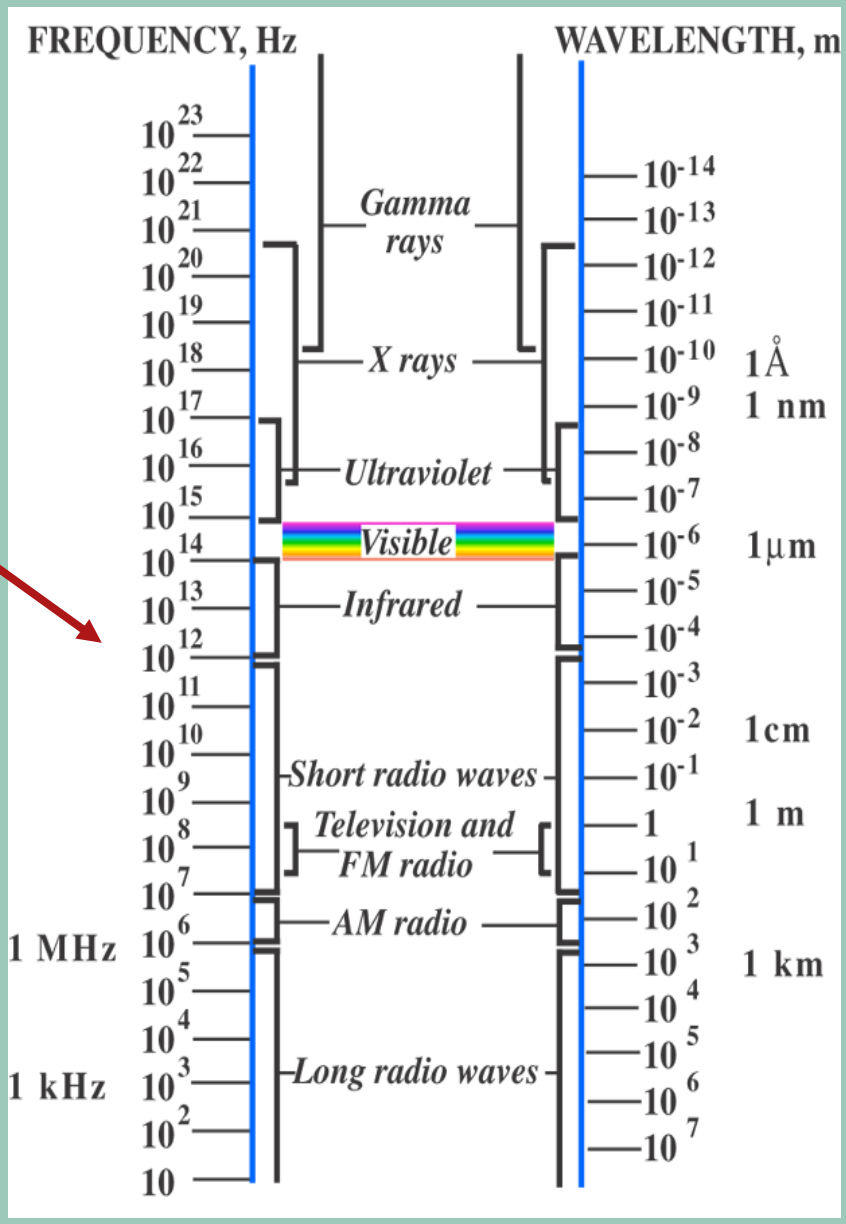


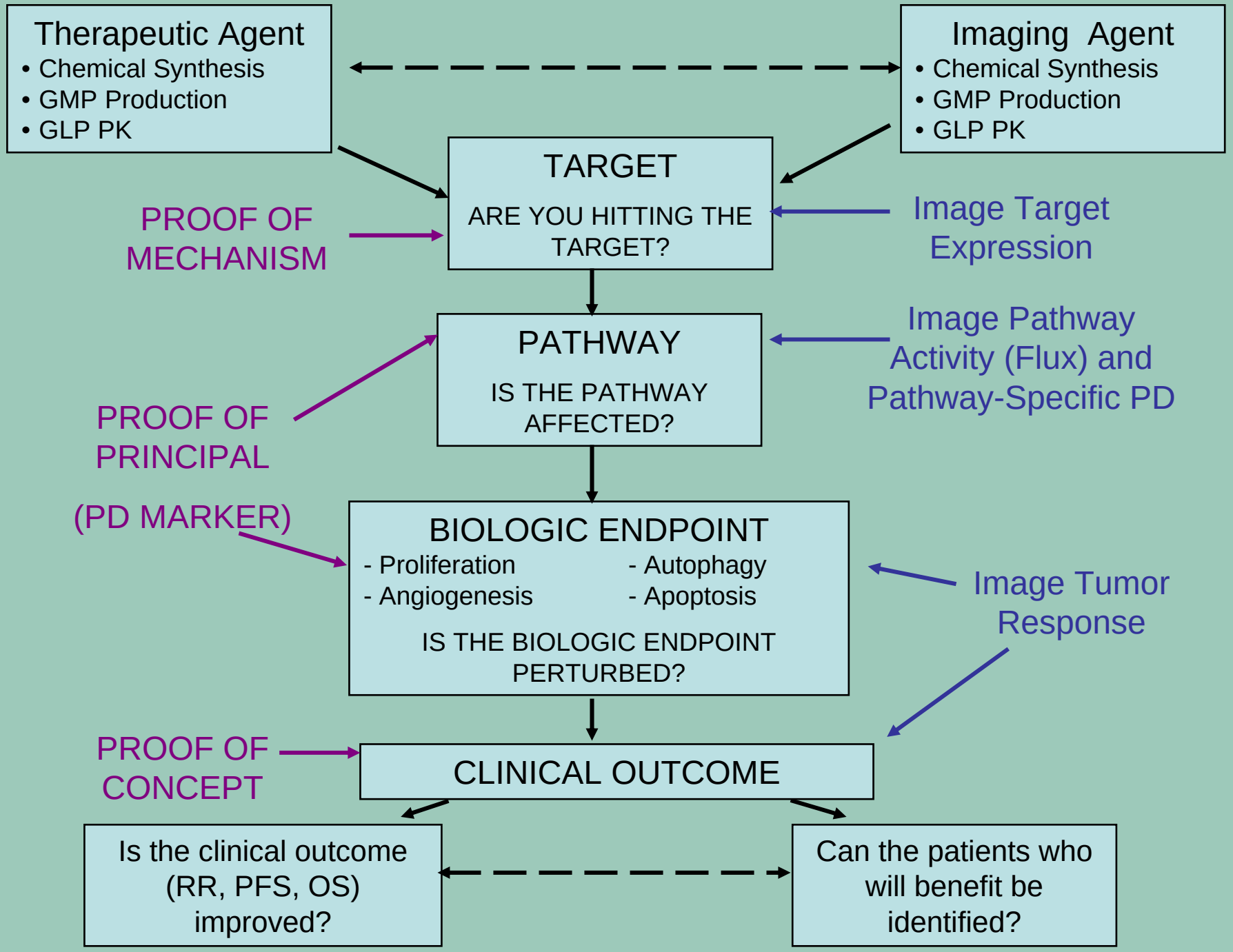


Massoud & Gambhir, Genes & Development, 2003

Molecular Imaging Agents






Therapeutic Agent
• Chemical Synthesis
• GMP Production
• GLP PK
Imaging Agent
• Chemical Synthesis
• GMP Production
• GLP PK
TARGET
ARE YOU HITTING THE TARGET?
PROOF OF MECHANISM
Image Target Expression
PATHWAY
IS THE PATHWAY AFFECTED?
PROOF OF PRINCIPAL
Image Pathway Activity (Flux) and Pathway-Specific PD
(PD MARKER)
BIOLOGIC ENDPOINT
- Proliferation
- Angiogenesis
- Autophagy
- Apoptosis
IS THE BIOLOGIC ENDPOINT PERTURBED?
Image Tumor Response
PROOF OF CONCEPT
CLINICAL OUTCOME
Is the clinical outcome (RR, PFS, OS) improved?
Can the patients who will benefit be identified?

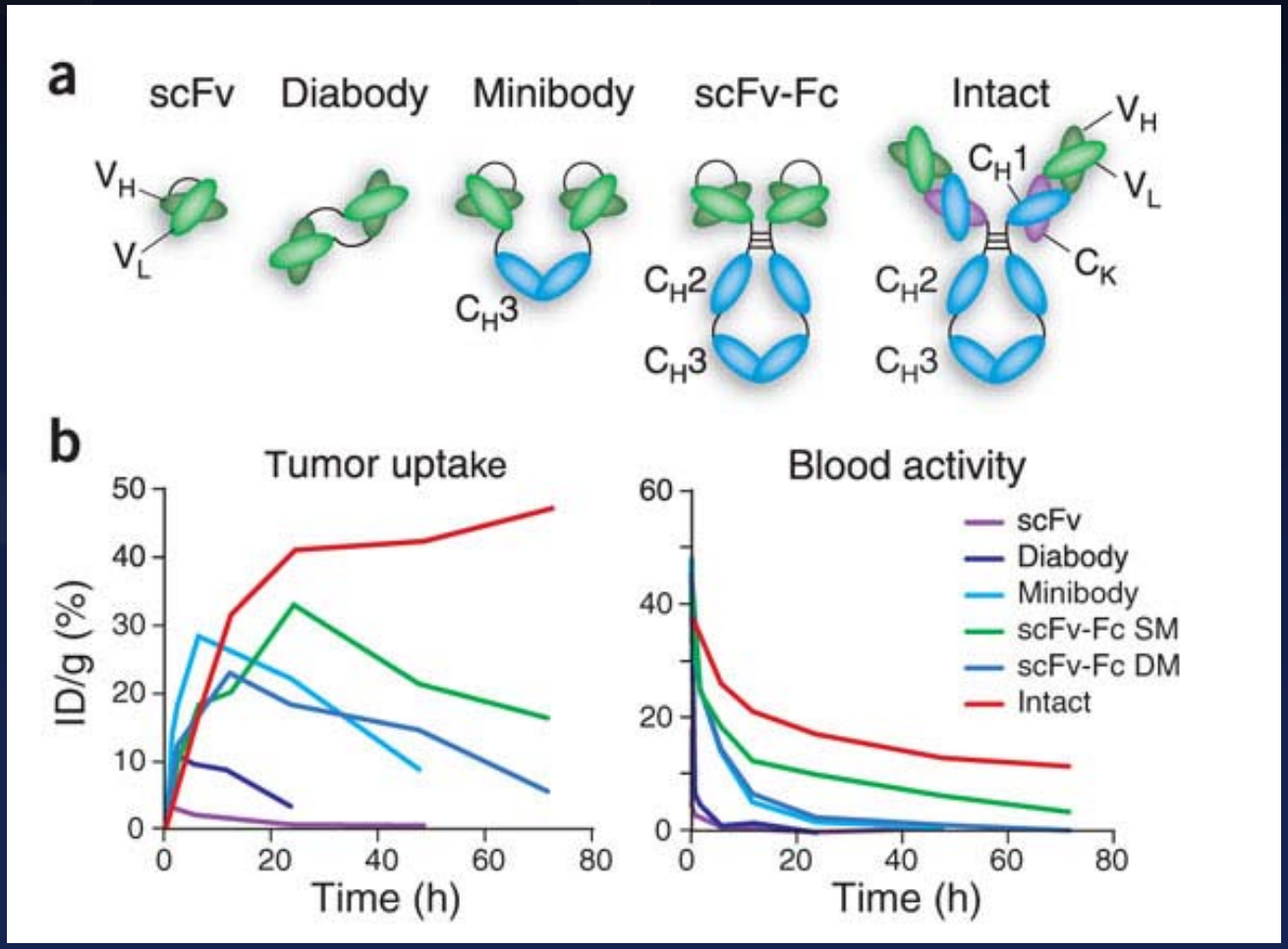
Imaging Pathway:

Molecular Imaging of PSCA in Prostate Cancer

Abstracts: *134 (Robert E. Reiter M.D. et. al., UCLA)*

Engineered Antibody Fragments

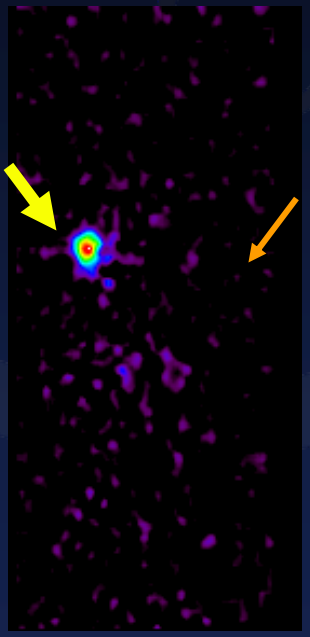
Engineering antibody fragments to control PK



A. Wu and P. Senter, Nature Biotech. 2005

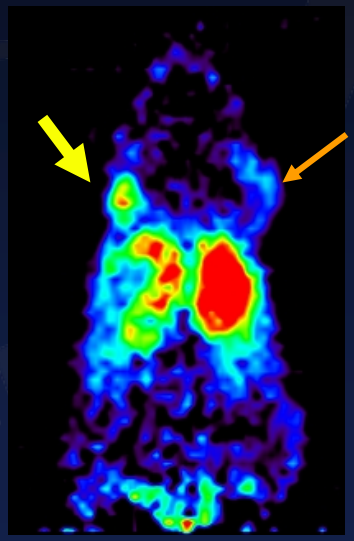
Antibody Engineering for *In vivo* Targeting

CEA



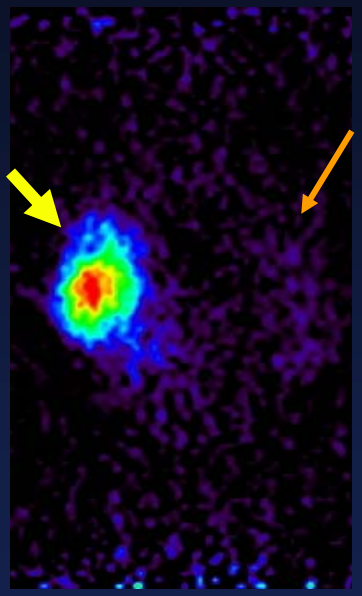
I-124 cT84.66
diabody

Her2/neu



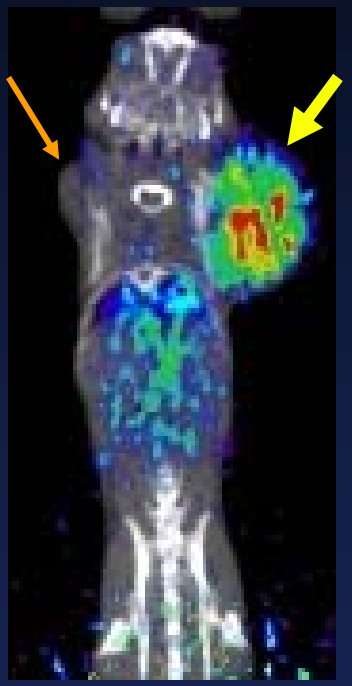
Cu-64-DOTA
Trastuzumab
scFv-Fc DM

CD20



I-124
Rituximab
minibody

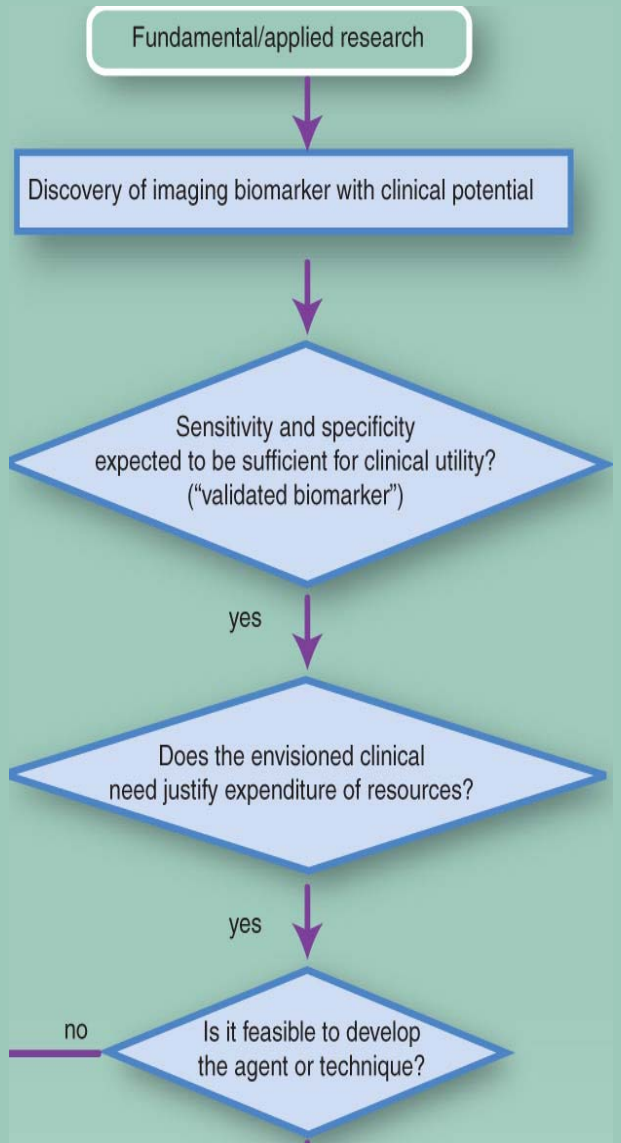
PSCA



I-124 hu2B3
minibody

T. Olafsen, D. Betting, J. Timmerman, J. Leyton, R. Reiter, Z. Gu, A. Wu

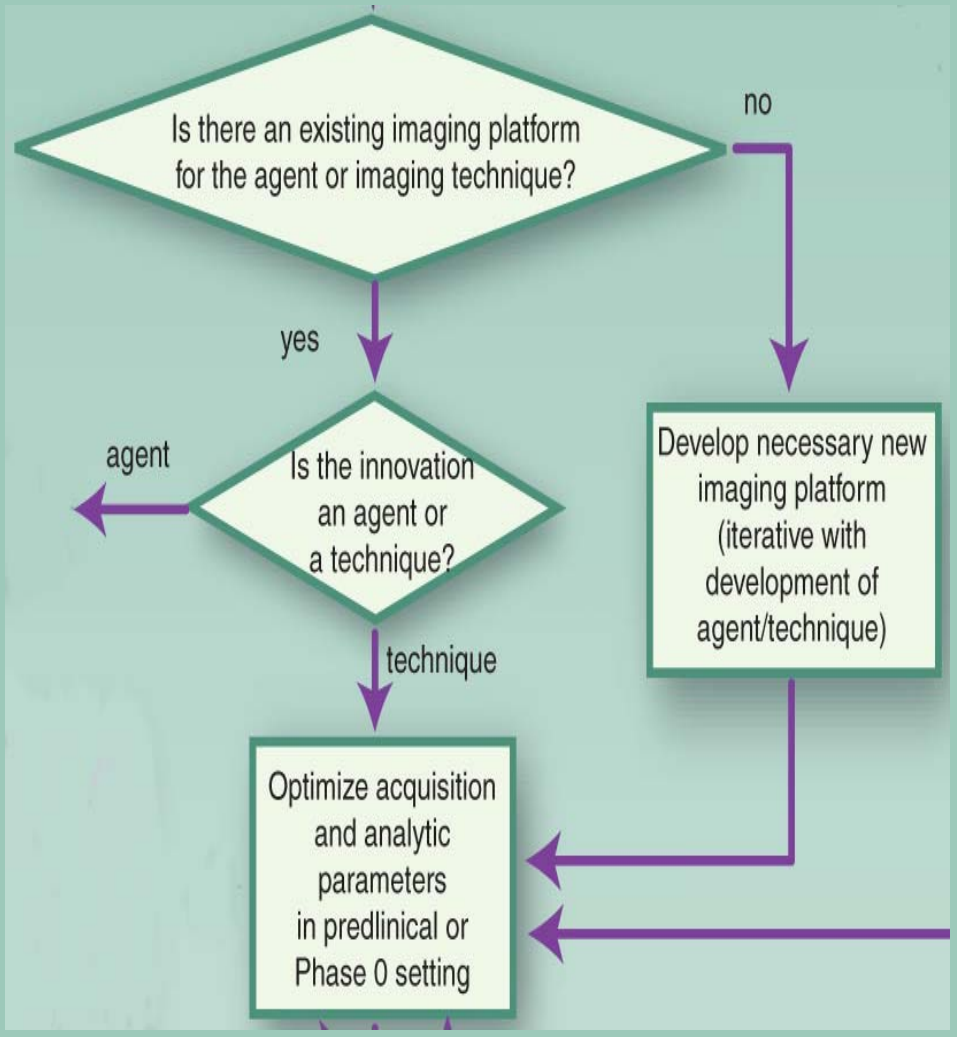
Imaging Pathway:
Credentialing: Scientific validation



- The prostate stem cell antigen (PSCA) is a prostate specific glycoprotein that is over-expressed in prostate cancer including androgen-independent prostate cancer. Alternate choices? Greater credentialing needed?
- Specificity likely sufficient if not imaging in the prostate bed. Sensitivity dependent on imaging technique and levels of receptor. What are levels of receptor in various tissue microarrays?
- Clinical need could include staging and monitoring response to therapies. Could be done in conjunction with a 99mTc-MDP Bone scan or a F- bone scan. Alternates of CT, MRI, MRS, ultrasound, Prostascint still not sufficient
- Feasible to develop engineered antibody fragments against PSCA which can then be radiolabeled for PET and/or SPECT imaging

  Also possible to label for non-radionuclide imaging (e.g., optical)

Imaging Pathway:
Creation of Modality



- Clinical PET-CT and clinical SPECT-CT already exist as imaging platforms
- Innovation is the molecular imaging agent in this case
- Consider different engineered antibody fragments (e.g., minibody or diabody)

Imaging Pathway:
Creation of Modality: radiolabeling

Perform radiolabeling dosimetry, etc.

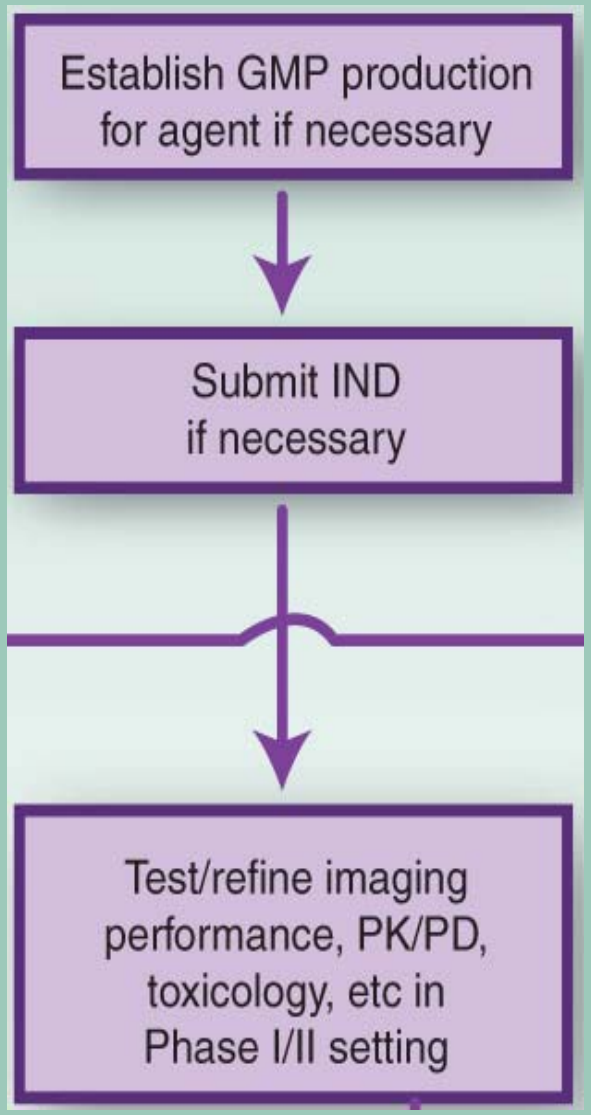
- Explore possible radiolabel choices relative to pharmacokinetics of the engineered antibody fragment. Possibly use 18F vs. 64Cu vs. 124I for PET and 99mTc for SPECT. Also other labels for other modalities.
- Dosimetry with each radioisotope needed in murine models. Possibly with second species?

Imaging Pathway:
Supporting tools:

Develop new assays or other supporting tools as necessary*

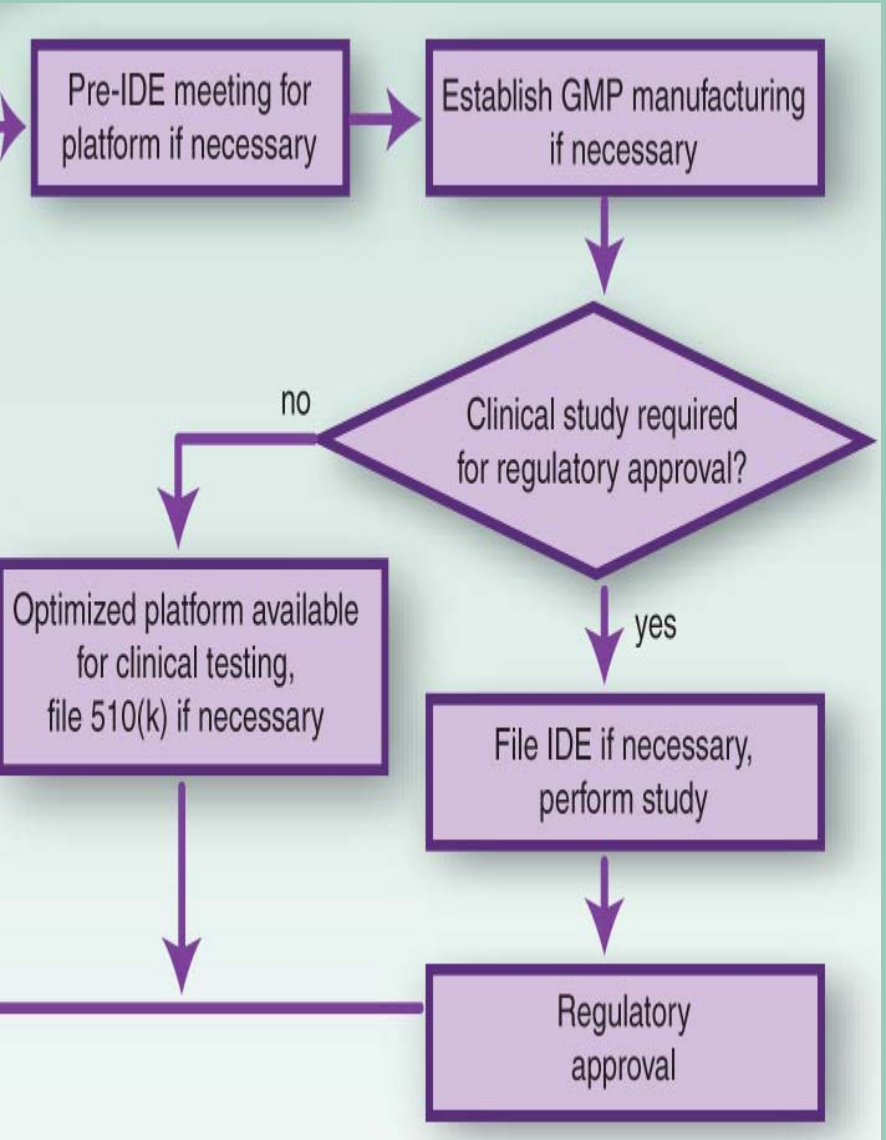
- Develop tracer kinetic models for imaging agent including how signal relates to levels of PSCA
- Mechanism for distribution of imaging agents
- Support instrumentation for automated synthesis and radiolabeling of imaging agents
- Develop physical phantoms which can also be imaged

Imaging Pathway:
Preclinical Development



- Establish GMP/GLP production of antibody fragment in scale-up
- Humanized Ab issues
- Establish dosimetry in pre-clinical models
- Establish toxicity in one species
- Submit eIND for a biologic if possible but also explore IND submission
- Perform Phase I human studies to look at radiation dosimetry and toxicity, optimal imaging times, biodistribution. Include blood sampling. Healthy volunteers vs. patients?

Imaging Pathway:
Preclinical Development



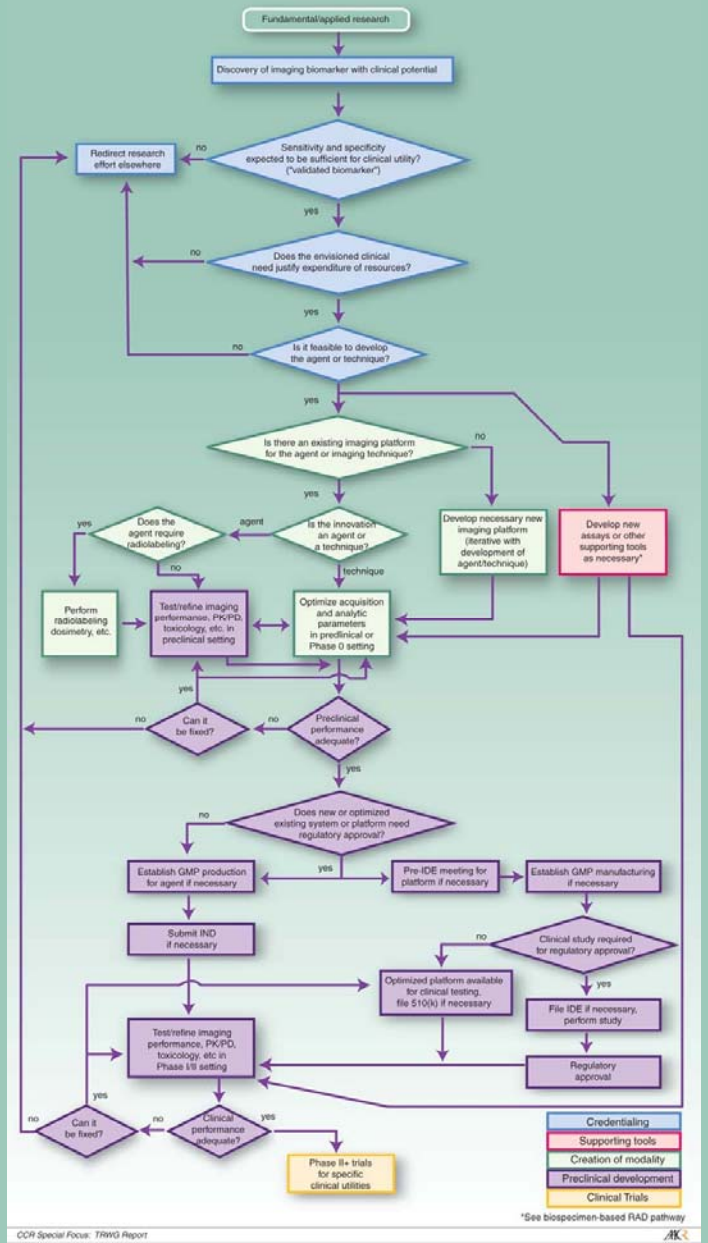
- No equipment approvals needed for this particular approach
- Obtain eIND/IND
- Discuss study with local RDRC if one exists

Imaging Pathway:
Clinical Trials

Phase II+ trials for specific clinical utilities

- Study PET-CT imaging in patients with prostate cancer with proven spread
  - Consider different entry criterion
- Compare to existing strategies including bone scanning and FDG PET-CT
- Understand limitations of detection in the prostate bed
- Pancreatic cancer imaging also possible
- Gold standard issues?
- Standardization of image protocols and acquisition across sites
- Work with ACRIN on multicenter trials

Imaging Pathway Summary



Credentialing of PSCA

Pre-clinical models with Engineered Ab Fragments

Preclinical Radiation Dosimetry and eIND filing

GMP/GLP production and Phase 1 Trial

Phase II Trials in Prostate Cancer